Twenty Dollars ($920.00) to cover the extension fee as required by 37 C.F.R. §§1.17(a)(3) and 1.136(a).

Submitted concurrently herewith is a Terminal Disclaimer pursuant to 37 C.F.R. §1.321(c) to obviate an obviousness-type double patenting rejection of record.

IN THE CLAIMS:

Cancel claims 19, 21 and 22.

REMARKS

I. Lineage of Referenced Application

The referenced application is a continuation of U.S. Patent Application Serial No. 09/187,277, filed November 6, 1998, now abandoned (the "'277 application"), which is a continuation of U.S. Patent Application Serial No. 08/899,931, filed July 24, 1997, now abandoned, which is a continuation of U.S. Patent Application Serial No. 08/376,512, filed January 23, 1995, now U.S. Patent No. 5,714,504, issued February 3, 1998 (the "'504 patent"), which is a continuation-in-part of U.S. Patent Application Serial No. 08/256,174, filed June 28, 1994 as a 35 U.S.C. §371 application of PCT/SE94/00509, filed May 27, 1994, now U.S. Patent No. 5,693,818, issued December 2, 1997 (the "'818 patent").

II. Claim Rejection – 35 U.S.C. §102(b)

Claims 1, 19, 21, 22 and 35 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Example 6 of US 4,738,974 to Brändström (the "'974 patent").

Example 6 of the '974 patent is directed to the preparation of di-omeprazole magnesium salt. Example 6 discloses that a solution of $Mg(OCH_3)_2$ in methanol was added dropwise to a solution of omeprazole in methanol. It is reported that evaporation gave a crystalline solid of the di-omeprazole magnesium salt.

The claimed invention is directed to the magnesium salt of the (-)-enantiomer of omeprazole in an optically pure form (claim 1) and in its crystalline form (claim 35). In contrast, the magnesium salt of omeprazole racemate is disclosed and claimed by the '974 patent (See Example 6). By definition, omeprazole racemate consists of equal shares of its (+)- and (-)-enantiomers. Therefore, the claimed magnesium salt of the (-)-enantiomer is a new and different compound when considered in view of the '974 patent.

The Examiner relies on a translation of Section 3.2 "Spontaneous resolution" from Seminars on Organic Synthesis", Vol. 18, (1958) by the Japanese Chemical Society. Specifically, in view of the cited Japanese reference, the Examiner alleges that it is known that spontaneous resolution occurs in the case of recrystallization of a racemic mixture. Accordingly, the Examiner concludes that it is conceivable that the prior art compound, e.g., Example 6 of the '974 patent, may possess the claimed optical purity.

The Examiner's attention is directed to the following disclosure from the cited Japanese reference:

> It is known that a spontaneous resolution occurs in the case of recrystallization of a racemic modification. For example, when 2,4-dioxo-2,3-diethyl-5-methylpiperidine is ***recrystallized 400 times*** from methanol-water, or acetone, it is separated into the antipodes...This is considered as a specific example of a spontaneous resolution occurring when a racemic modification forms a crystal...
>
> ***Although the success for this method is relatively rare, it is easy to try*** it because no reagents are need for resolution and the procedure used is simple. (Emphasis added).

Therefore, to achieve spontaneous resolution, the Japanese reference teaches that the compound had to be recrystallized 400 times! Moreover, the Japanese reference discloses that the success of spontaneous resolution is relatively low. As such, the Japanese reference is nothing more than a "suggestion to try" with an admitted low expectation of success. Thus, Applicants respectfully submit that it is improper to rely on the Japanese reference to interpret the disclosure of Example 6. Accordingly, the Examiner's reliance on the Japanese reference is misplaced. In stark contrast to the Japanese reference which discloses a recrystallization procedure that was repeated 400 times to obtain a spontaneous resolution, Example 6 of the '974 patent discloses a single recrystallization to achieve the product in racemic form.

For all of the foregoing reasons, it is submitted that the Japanese reference cannot properly be used to suggest that Example 6 of the '974 patent is an example of spontaneous resolution producing the claimed magnesium salt of the (-)-enantiomer of omeprazole. Instead, the Japanese reference supports Applicants' position that the '974 patent does not teach spontaneous resolution and that the claimed magnesium salt of the (-)-enantiomer of omeprazole is a new and different compound when considered in view of Example 6 of the '974 patent.

Withdrawal of the §102(b) rejection in view of the '974 patent is requested.

III. Claim Rejection – 35 U.S.C. §103(a)

Claims 1, 19, 21, 22 and 35 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the '974 patent and DE 4 035 455 (DE '455) for the reasons of record.

In summary, the Examiner states that the Declaration of Tommy Andersson is unpersuasive because it allegedly fails to show an unexpected result. Specifically, the Examiner

alleges that it was expected that stereoisomers of omeprazole would exhibit different activities. The Examiner relies on the Knabe reference for the alleged disclosure that biological systems are known to respond to stereospecificity.

It is to be noted that omeprazole, whether the racemate or either enantiomer, is only a ***prodrug***. Accordingly, omeprazole in itself is inactive. The actual drug, sulfenamide, is formed in the body of the patient in the parietal cells of the stomach. Sulfenamide is not a chiral compound. This was known well before May 28, 1993, i.e., the priority date of the subject application. In this regard, the Examiner's attention is directed to the publication, P. Lindberg et al., "Omeprazole: The First Proton Pump Inhibitor", Medicinal Research Reviews **10** (1990) 2-50 ("Lindberg"), which was cited in an Information Disclosure Statement, filed February 12, 1997, in the great-grandparent application serial no. 08/376,512, which issued as the '504 patent. The Lindberg publication at Figure 9b on page 14 shows the proton-catalyzed rearrangement of omeprazole to the non-chiral sulfenamide.

The Examiner's attention is directed to another publication, P. Erlandsson et al., "Resolution of the enantiomers of omeprazole", Journal of Chromatography **532** (1990) 305-319 ("Erlandsson"), which was cited in an Information Disclosure Statement, filed November 7, 1994, in the great-great-grandparent application serial no. 08/256,174, which issued as the '818 patent. The following disclosure appears at page 305 of Erlandsson:

> The findings of mechanistic studies have shown that omeprazole is not per se the active inhibitor, but itself activated in vivo within the acid compartments of the parietal cell to an achiral sulphenamide [2]. ***One should thus expect that the two enantiomers of omeprazole have the same acid inhibitory effect at a cellular level.*** However, the fact that the enantiomers separate on chromatography using human (HAS) and bovine serum albumin (BSA) [3,4] may indicate a difference in the degree of plasma protein binding of the two enantiomeric forms. (Emphasis added).

Erlandsson investigated the properties of omeprazole and its enantiomers. The results are reported on page 318 as follows:

> Thus, in similarity with the racemate both enantiomers were found to inhibit acid secretion in this model. To statistically compare the effects of the three drugs a Newman-Keuls multiple range test of the IC_{50} values obtained from the five different experiments was performed. This test showed a difference between omeprazole and the (+)-enantiomer (significance level, $p = 0.05$). However, ***the IC_{50} values of the (+)-enantiomer did not differ from those of the (-)-enantiomer at this significance level, and omeprazole was accepted as equal in potency to the (-)-enantiomer.*** In conclusion, the inhibitory effect of acid formation in the isolated glands of the racemate (H166/68) should be ascribed to the inhibitory action of both of its enantiomers. (Emphasis added).

Therefore, at the time the claimed invention was made and contrary to the Knabe reference, it was expected that (+)- and (-)-enantiomers of omeprazole would not differ considerably quantitatively and qualitatively. Accordingly, it was unexpected that the claimed magnesium salt of the (-)-enantiomer of omeprazole is defined by a different and more advantageous pharmacokinetic profile in comparison to either the racemic form of omeprazole or the magnesium salt of omeprazole.

A determination of obviousness cannot be merely made on the basis that a qualitative difference in pharmacological properties would have been expected. The Examiner must also consider ***the degree of qualitative improvement***. In this regard, Applicants submit that the comparative data set forth in the Declaration of Tommy Andersson shows ***a greater than expected improvement*** with respect to a number of properties which include (a) higher dose efficiency, (b) less interindividual variation in AUC and (c) longer duration of elevated intragastric pH which is obtained with the claimed invention. It is precisely this type of "greater than expected result" which has long been an evidentiary factor pertinent to a finding on nonobviousness (*United States v. Adams*, 383 U.S. 39, 51-52 (1966)).

Neither the '974 patent nor the DE '455 reference suggests the advantageous and distinguishing properties which characterize the claimed magnesium salt of the (-)-enantiomer of omeprazole. For all of the foregoing reasons, withdrawal of the rejections under 35 U.S.C. §103(a) is requested.

IV. Claim Rejection - 35 U.S.C. §101

Claims 1, 19, 21, 22 and 35 are rejected under 35 U.S.C. §101 as claiming the same invention as that of claims of the '974 patent and US 5,900,424 to Källström et al. ("' the '424 patent).

The term "same invention", as contemplated by 35 U.S.C. §101, means an invention drawn to identical subject matter. *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed, Cir. 1985). The test is whether the claims of the application and cited patent cover the same thing. *Carman Induc., Inc. V. Wahl*, 724 F.2d 932, 220 U.S.P.Q. 481 (Fed. Cir. 1983).

With regard to the §101 rejection based on the '974 patent, Applicants rely on the arguments in Section II, above. The claimed invention is directed to the magnesium salt of the (-)-enantiomer of omeprazole In contrast, the magnesium salt of omeprazole racemate is disclosed and claimed by the '974 patent. The '974 patent does not teach spontaneous resolution. Thus, the claimed magnesium salt of the (-)-enantiomer of omeprazole is a new and different compound when considered in view of the '974 patent. Accordingly, there is no identity of invention between claims 1 and 35 of the claimed invention and the claims of the '974 patent.

Claim 1 of the '424 patent defines a magnesium salt of omeprazole racemate having a degree of crystallinity which is higher than 70% as determined by x-ray powder diffraction. In

contrast, the claimed compound is directed to the magnesium salt of the (-)-enantiomer of omeprazole.

Omeprazole racemate consists of equal shares of its (+)- and (-)-isomers and the racemic mixture is defined by a set of physical and chemical properties. As demonstrated by the Declaration of Andersson, the pharmacokinetic profile of (-)-omeprazole is distinguishable from that of the racemate. The different pharmacokinetic and metabolic profile relative to the (-)-enantiomer and racemate, respectively, suggests a lack of identity as required by 35 U.S.C. §101. Even if for the sake of argument, the (-)-enantiomer of omeprazole is considered to be a part of omeprazole, there is still a lack of identity since the claimed magnesium salt of the (-)-enantiomer is a new chemical entity vis-à-vis the compound of the '424 patent.

Therefore, the double patenting rejection based on the '424 patent is improper and should be withdrawn.

V. Claim Rejection – 35 U.S.C. §§102(f) and (g)

Claims 1, 19, 21, 22 and 35 are alleged to be directed to the same invention as that of claims of the commonly assigned '974 and '424 patents. The Examiner states that the alleged issue of priority under 35 U.S.C. §102(g) and possibly (f) of this single invention must be resolved. Applicants are required to state which entity is the prior inventor of the alleged conflicting subject matter.

Applicants rely on the arguments in Sections II and IV, above. Claims 1 and 35 of the claimed invention are novel and not identical when compared to the '974 and '474 patents, respectively. Specifically, claims 1 and 35 of the application are directed to the magnesium salt of the (-)-enantiomer of omeprazole in an optically pure form (claim 1) and in its crystalline form

(claim 35). In contrast, the magnesium salt of omeprazole racemate is disclosed and claimed by the '974 patent The '974 patent does not teach spontaneous resolution. The claimed magnesium salt of the (-)-enantiomer of omeprazole is a new and different compound when considered in view of Example 6 of the '974 patent. Accordingly, there is no identity of invention between claims 1 and 35 of the claimed invention and the claims of the '974 patent.

Furthermore, as demonstrated by the Declaration of Andersson, the different pharmacokinetic and metabolic profile relative to the (-)-enantiomer of omeprazole and omeprazole racemate suggests that the claims of the application and the '424 patent do not cover the same thing as required by 35 U.S.C. §101. Accordingly, there is a lack of identity since the claimed magnesium salt of the (-)-enantiomer is a new chemical entity vis-à-vis the compound of the '424 patent.

VI. Claim Rejection – 35 U.S.C. §101

Claims 19, 21 and 22 are rejected under 35 U.S.C. §101 as claiming the same invention as that of claims of US 5,877,192 to Lindberg et al. (the "'192 patent") and US 5,714,504 to Lindberg et al. (the "'504 patent").

Claims 19, 21 and 22 have been canceled. Therefore, the rejection is moot and withdrawal thereof is requested.

VII. Claim Rejection – Obviousness-type Double Patenting

Claims 1, 19, 21, 22 and 35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of the '974, '192 and '504 patents.

Submitted concurrently herewith is a Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c) to obviate the obviousness-type double patenting rejection with respect to the '192 and '504 patents. Withdrawal of the rejection as to the '192 and '504 patents is requested.

With specific regard to the '974 patent, Applicants respectfully submit that the obviousness-type double patenting rejection is contrary to the guidelines set forth in M.P.E.P. §804(II)(B)(1). An obviousness-type double patenting rejection is appropriate when any claim in the application defines an invention that is ***merely an obvious variation*** of an invention claimed in the patent. An obviousness-type double patenting rejection is analogous to the nonobviousness requirement of 35 U.S.C. §103. As such, the analysis employed in an obviousness-type double patenting determination must be based on the factual inquiries set forth in *Graham v. John Deere Co., 383 U.S. 1, 148 U.S.P.Q.4589 (1966).* Therefore, the Examiner is required to consider any objective indicia of nonobviousness, such as unexpected results.

In this regard, Applicants rely on the arguments set forth in Section III, above, in connection with the §103 rejection based on the '974 patent. Specifically, at the time the claimed invention was made it was expected that (+)- and (-)-enantiomers of omeprazole would not differ considerably quantitatively and qualitatively. In view of the Lindberg and Erlandsson publications, the person of ordinary skill in the art would have expected (+)- and (-)-enantiomers of omeprazole to be equal in potency. Thus, the advantageous pharmacological properties of the claimed compound are indeed unexpected.

Moreover, the claimed magnesium salt of the (-)-enantiomer of omeprazole is defined by a different and more advantageous pharmacokinetic profile when compared either directly or indirectly, whatever the case may be, to either the racemic form of omeprazole or the magnesium salt of omeprazole. The Declaration of Tommy Andersson shows ***a greater than expected***

improvement in (a) higher does efficiency, (b) less interindividual variation in AUC and (c) longer duration of elevated intragastric pH which is obtained with the claimed invention. In view of the evidence of a greater than expected improvement, the claimed invention is more than just an obvious variation of the cited prior art. Withdrawal of the obviousness-type double patenting rejection based on the '974 patent is requested.

VIII. Provisional Claim Rejection – Obviousness-type Double Patenting

Claims 1, 19, 21, 22 and 35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims of co-pending Application Serial No. 09/077,719 (the "'719 application"), now US 6,369,085 to Cotton et al., issued April 9, 2002 (the '085 patent).

The '085 patent discloses and claims the magnesium salt of S-omeprazole trihydrate. The expression "S-omeprazole" is interchangeable with "the (-)-enantiomer of omeprazole". ***The compounds of the '085 patent, i.e., the magnesium salt of S-omeprazole trihydrate, is substantially free from magnesium salts of R-omeprazole and other forms of the magnesium salt of S-omeprazole (See the '085 patent at col. 2, lines 30-37).*** The magnesium salt of S-omeprazole trihydrate of the '085 patent is uniquely characterized by an X-ray powder diffractogram (See claim 1). Moreover, it was demonstrated with data comparative submitted during the examination of the '719 application, that the magnesium salt of S-omeprazole trihydrate is more stable after 6 and 12 months than the prior art magnesium salt of S-omeprazole dihydrate.

As previously stated in Section VII, above, an obviousness-type double patenting rejection is appropriate when any claim in the application defines an invention that is ***merely an***

obvious variation of an invention claimed in the patent. An obviousness-type double patenting rejection is analogous to the nonobviousness requirement of 35 U.S.C. §103. As such, the analysis employed in an obviousness-type double patenting determination must be based on the factual inquiries set forth in *Graham v. John Deere Co., 383 U.S. 1, 148 U.S.P.Q.4589 (1966)*. Therefore, the Examiner is required to consider any objective indicia of nonobviousness, such as unexpected results.

The compounds of the '085 patent, i.e., the magnesium salt of S-omeprazole trihydrate, is substantially free from magnesium salts of R-omeprazole and other forms of the magnesium salt of S-omeprazole. Moreover, the improved stability of the compounds of the '085 patent is not suggested by the referenced application. Applicants submit that the improved stability of the compounds of the '085 is evidence that the difference between the claimed subject matter of the subject application and the '085 patent, respectively, is more than just an obvious variation.

Accordingly, for all of the foregoing reasons, the obviousness-type double patenting rejection is improper and withdrawal thereof is requested.

CONCLUSION

Applicants have made a good faith attempt to respond to the Office Action. Claims 1 and 35 are directed to patentable subject matter. Accordingly, Applicants request reconsideration and allowance of the claims.

Any additional fee due in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: May 29, 2002

Respectfully submitted,

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